



# UNITED STATES PATENT AND TRADEMARK OFFICE

*[Signature]*  
UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,286	04/20/2001	Jacques Dumas	BAYER-14	9096
23599 7590 11/16/2007 MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			EXAMINER KWON, BRIAN YONG S	
			ART UNIT 1614	PAPER NUMBER
			MAIL DATE 11/16/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Art Unit: 1614

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/838,286

Filing Date: April 20, 2001

Appellant(s): Jacques Dumas

MAILED  
NOV 16 2007  
GROUP 1600

---

Jacques Dumas  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the Appellant's Reply Brief filed August 03, 2007.

**(1) *Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

**(2) *Related Appeals and Interferences***

The brief contains a statement concerning related appeals or interferences.

**(3) *Status of Claims***

The statement of the status of the claims contained in the brief is correct

This appeal involves claims 50 and 52-56.

**(4) *Status of Amendments***

No amendment after final has been filed.

**(5) *Summary of Claimed Subject Matter***

The summary of claimed subject matter contained in the brief is correct.

**(6) *Grounds of Rejection to Be Reviewed on Appeal***

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is not correct.

The grounds for rejection to be reviewed are:

(1) the rejection of claims 50 and 52-56 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (e.g., rheumatoid arthritis, osteoarthritis and septic arthritis) by administration of the specific compounds of the Formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host" or "the treatment of a disease other than cancer" with the administration of "a compound of Formula I". This rejection is set forth in prior Office Action, mailed 06/28/2006.

(2) the provisional rejection of claims 50 and 52-56 under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776, 935 or claims 1, 3-4 and 7-11 of copending US. Application No. 10/086417. This rejection is set forth in prior Office Action, mailed 06/28/2006.

**(7) *Claims Appendix***

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) *Evidence Relied Upon***

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Chialda et al., Respiratory Research 2005, 6:36, pp. 1-19.

Art Unit: 1614

Kapoun et al. Molecular Pharmacology, abstract, 2006. [www.mopharmaspetjournals.org](http://www.mopharmaspetjournals.org).

Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773.

Cecil Textbook of Medicine 20<sup>th</sup> Edition, Vol. 1, Bennett et al., 1997.

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9<sup>th</sup> ed., 1996, pp. 51-58.

Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, pp.2047-2050.

Blink et al., The American Association of Immunologists, 2001, 166:582-587.

Gura et al., Science, 1997, 278:1041-1042.

Johnson et al., British J. of Cancer, 2001, 84(10):1424-1431.

**(9) *Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

Claims 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (e.g., rheumatoid arthritis, osteoarthritis and septic arthritis) by administration of the specific compounds of the Formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host" or "the treatment of a disease other than cancer" with the administration of "a compound of Formula I".

The claims 1-9 and 52-55 are drawn to a method for treating a disease mediated by p38 within a host, said method comprising to said host a compound of Formula I:

Art Unit: 1614

A - D - B

(I)

or a pharmaceutically acceptable salt thereof, wherein

D is  $\text{-NH-C(O)-NH-}$ ,

A is a

substituted t-butylpyridinyl, unsubstituted t-butylpyridinyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl, substituted quinolinyl or unsubstituted quinolinyl, and

B is a substituted or unsubstituted, phenyl naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl or a bridged cyclic structure of the formula  $\text{-L(ML}^1\text{)}_q$ , wherein q is an integer of 1-3, and  $\text{L}^1$  and L are each independently thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl substituted quinolinyl, isoquinolinyl or substituted isoquinolinyl and M is  $\text{-O-}$ ,  $\text{-CH}_2\text{-}$ ,  $\text{-S-}$ ,  $\text{-NH-}$ ,  $\text{-C(O)-}$ ,  $\text{-O-CH}_2\text{-}$  or  $\text{-CH}_2\text{-O-}$ , with cyclic structure L bound directly to D,

wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and  $\text{W}_n$ , where n is 0-3 and each W is independently selected from the group consisting of

$\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkoxy,  $\text{C}_{3-10}$  cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O;  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{1-10}$  alkenoyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_7\text{-C}_{24}$  aralkyl,  $\text{C}_3\text{-C}_{12}$  heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S,  $\text{C}_4\text{-C}_{24}$  alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted  $\text{C}_{1-10}$  alkyl, substituted  $\text{C}_{1-10}$  alkoxy, substituted  $\text{C}_{3-10}$  cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted  $\text{C}_{2-10}$  alkenyl, substituted  $\text{C}_{1-10}$  alkenoyl, substituted  $\text{C}_6\text{-C}_{14}$  aryl, substituted  $\text{C}_7\text{-C}_{24}$  alkaryl, substituted  $\text{C}_7\text{-C}_{24}$

Art Unit: 1614

aralkyl, substituted C<sub>3</sub>-C<sub>12</sub> heteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S, substituted C<sub>4</sub>-C<sub>24</sub> alkylheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

-CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7'</sup>, -C(O)-R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7'</sup>, -NR<sup>7</sup>C(O)OR<sup>7'</sup>, -NR<sup>7</sup>C(O)R<sup>7'</sup>, with each R<sup>7</sup> and R<sup>7'</sup> independently selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, up to per halosubstituted C<sub>1-10</sub> alkyl, up to per halosubstituted C<sub>1-10</sub> alkoxy, up to per halosubstituted C<sub>2-10</sub> alkenyl and up to per halosubstituted C<sub>1-10</sub> alkenoyl, C<sub>3-10</sub> cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C<sub>6-14</sub> aryl, C<sub>3-10</sub> hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C<sub>3-10</sub> cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C<sub>6-14</sub> aryl and up to per halo substituted C<sub>3-10</sub> hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7'</sup>, -C(O)-R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7'</sup>, -NR<sup>7</sup>C(O)OR<sup>7'</sup>, and -NR<sup>7</sup>C(O)R<sup>7'</sup>, wherein R<sup>7</sup> and R<sup>7'</sup> are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J<sub>n</sub>, where n is 0-3 and each J is independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7'</sup>, -C(O)-R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7'</sup>, -NR<sup>7</sup>C(O)OR<sup>7'</sup>, -NR<sup>7</sup>C(O)R<sup>7'</sup>, with each R<sup>7</sup> and R<sup>7'</sup> independently as defined for W above, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, C<sub>3-10</sub> cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-14</sub> aryl, C<sub>3-12</sub> hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C<sub>7-24</sub> aralkyl, C<sub>7-24</sub> alkaryl, C<sub>4</sub>-C<sub>23</sub> alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C<sub>1-10</sub> alkyl, substituted C<sub>1-10</sub> alkoxy, substituted C<sub>3-10</sub> cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C<sub>2-10</sub> alkenyl, substituted C<sub>1-10</sub> alkenoyl, substituted C<sub>6-14</sub> aryl, substituted C<sub>3-12</sub> hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C<sub>7-24</sub> alkaryl, substituted C<sub>7-24</sub> aralkyl and substituted C<sub>4</sub>-C<sub>23</sub> alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S,

Art Unit: 1614

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -COR<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7'</sup>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7'</sup>, -NR<sup>7</sup>C(O)R<sup>7'</sup>, and -NR<sup>7</sup>C(O)OR<sup>7'</sup>, with R<sup>7</sup> and R<sup>7'</sup> as defined above for W.

Further limitations include "A has 1-3 substituents selected from the group consisting of C1-10 alkyl, up to per halo substituted C1-10 alkyl, -CN, -OH, halogen, C1-10 alkoxy, up to per halo substituted C1-10 alkoxy and C3-10 heterocyclic moieties having at least 5 cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur" (claim 52); "L1 is substituted 1 to 3 times by one or more substituents selected from the group consisting of -CN, halogen up to per halo, C1-10 alkyl, C1-10 alkoxy, -OH, up to per halo substituted C1-10 alkyl, up to per halo substituted C1-10 alkoxy, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7'</sup>, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7'</sup>, -C(O)R<sup>7</sup> or -NO<sub>2</sub>, wherein each R<sup>7</sup> and R<sup>7'</sup> is independently selected from hydrogen, C1-10 alkyl, C1-10 alkoxy, C2-10 alkenyl, C1-10 alkenoyl, up to per halo substituted C1-10 alkyl, up to per halo substituted C1-10 alkoxy, up to per halo substituted C2-10 alkenyl and up to per halo substituted C1-10 alkenoyl" (claim 53); "a pharmaceutically acceptable salt of a compound of formula I is administered which is selected from the group consisting of a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth

Art Unit: 1614

cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations” (claim 54); “the treatment of a disease other than cancer” (claim 55); “the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelating disease of the nervous system” (claim 56).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (i.e., rheumatoid arthritis, osteoarthritis and septic arthritis) by the specific compounds of the formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for “a method of treating a disease mediated by p38 within a host”, “the treatment of a disease other than cancer” with “a compound of Formula I”. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.



The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I.

The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations including arthritis, rheumatic fever, bone resumption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, end toxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Cohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, Pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including *Plasmodium falciparum* malaria and cerebral malaria, non-insulin-dependent diabetes

Art Unit: 1614

mellitus DM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis including systemic complications in acute pancreatitis, impaired wound healing infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (alliterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaka's disease resulting from Trypanosome cruse infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enter toxin A resulting from staphylococcus infection, meningococcal infection, and infections from *Borealis burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV) and subsequently administering the instantly claimed plethora of compound(s) represented by the formula. See the instant specification, page 4, lines 30-31; page 5, lines 18-31; page 6, lines 14-26; page 6, line 27 through page 7, line 23.

The specification discloses that because inhibition of p38 leads to inhibition of cytokines (e.g., Tiff production, IL-1 and IL-8) and inhibition of proteolysis enzymes (e.g., MMP-1 and

Art Unit: 1614

MMP-3) production, p38 inhibitors are useful in the treatment of above diseases or conditions encompassed by the instant claims.

With respect to the scope of enablement for the treatment of diseases mediated by p38,

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “silver bullet” is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, the art doubts that the inhibition of p38 is useful for the treatment of the instantly claimed disease condition, for example asthma (Chialda et al., Respiratory Research 2005, 6:36, pp. 1-19) and interstitial lung diseases and pulmonary fibrosis (Kapoun et al., Molecular Pharmacology, abstract, 2006, [www.molpharmaspetjournals.org](http://www.molpharmaspetjournals.org)).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

In addition, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein ‘evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to

disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the art is high. Thus, based on the state of art knowledge, one having ordinary skill in the art would not have expected that the administration of said compounds would be able to treat all of disease condition encompassed by the instant claims. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity when and/or after administering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51, in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interaction require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and the "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51). In the instant case, in the absence of fully recognizing the identify of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug

Art Unit: 1614

interactions occurring with many combinations of any compounds having the claimed functional properties in the pharmaceutical compositions herein. Thus, the teachings of Goodman & Gilman (in light of above mentioned Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773) clearly support that the instant claimed invention is highly unpredictable.

As mentioned above, the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism. The specification discloses that inhibition of p38 inhibits both cytokine production (eg.,  $\text{TNF}\alpha$ , IL-1, IL-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3). See page 2, lines 10-13. The specification correlates to various diseases that are related to excessive levels of  $\text{TNF}\alpha$ , excess or undesired matrix-destroying metalloprotease (MMP) activity or an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases. See page 2, line 14 thru page 5, line 17.

The specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of  $\text{TNF}\alpha$  production (page 75). However, the guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited.

As stated above, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of disease condition encompassed by the instant claim. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit

Art Unit: 1614

p38, but which compounds actually treat all of diseases mediated by p38 mechanism without undue amount of experimentation.

Since the efficacy of the claimed compounds in treating all of complex diseases condition may have unrelated manifestation mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "compound for Formula I",

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, it is known that the modification of urea core group with different substituents would have different physiological activity. For example, deletion of the two chlorine atoms or replacement of the chlorine atoms by methyl group in substituted phenyl ring attached to urea results in inactive compounds or weaker compound (Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, 2047-2050).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, one having ordinary skill in the art would not have predicted that all of the compounds represented by the instant formula would provide the claimed therapeutic utility without undue amount of experimentation.

The breadth of the claims encompasses plethora of compound(s) represented by the formula (over thousands compounds).

The instant specification discloses the preparation or synthesis of the instant compounds represented by the Formula I by known chemical reactions and procedures (page 18, line 3 thru page 22, line 2; page 29, line 3 thru page 74, line 3). Furthermore, the specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNF $\alpha$  production (page 75).

Although the specification provide sufficient guidance in how to make compounds that are suitable for the claimed invention, the specification fails to provide sufficient clarity in how to use it. The specification provides no guidance, in the way of enablement for the full scope of all compounds that are potentially suitable for the invention work similarly without known toxicity concern. The skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention **without undue amount of experimentation**.

As discussed above, none of the specification provides enabling disclosure for the full scope of all compounds that would behave similar without known toxicity concern. There is no demonstrated correlation that the tests and results apply to the claimed utility embraced by the instant claims.

Since the efficacy of the claimed compounds in treating all of complex diseases condition by all of compounds encompassed by the instant invention cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776,935



Art Unit: 1614

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 1, 3-4 and 7-11 of copending U.S. Application No. 10/086417.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed

invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

**(10) *Response to Argument***

Appellant's arguments and remarks filed February 02, 2007 and August 03, 2007 have been carefully considered, but are not deemed to be persuasive.

Appellant in his argument filed on August 03, 2007 takes the position that there is no evidence has been presented by the examiner that the identification of diseases mediated by p38 to be treated with the claimed compound is complex. Appellant alleges that the large number of diseases already identified by those skilled in the art as mediated by p38 is inconsistent with this allegation.

As discussed above, pharmaceutical art is highly unpredictable. Determining if any particular claimed compound would treat any particular diseases would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with to treat said disease conditions or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is large quantity of experimentation. In the instant case the instant invention encompasses anticipating the treatment of multiple complex disorders having unrelated manifestations including arthritis, rheumatic fever, bone resumption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, end toxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Cohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress

Art Unit: 1614

syndrome, acute pulmonary fibrotic disease, Pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including *Plasmodium falciparum* malaria and cerebral malaria, non-insulin-dependent diabetes mellitus DM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis including systemic complications in acute pancreatitis, impaired wound healing infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (alliterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaka's disease resulting from *Trypanosome* cruse infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enter toxin A resulting from *staphylococcus* infection, meningococcal infection, and infections from *Borealis burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV). See the instant specification, page 4, lines 30-31; page 5, lines 18-31; page 6, lines 14-26; page 6, line 27 thru page 7, line 23. Each of the above diseases is drawn to the treatment of

Art Unit: 1614

totally different conditions and would appear to seek results that differ depending on what diseases or conditions is being treated.

For instance, inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but

Art Unit: 1614

instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially Streptococcus pyogenes, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and Mycoplasma pneumoniae. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). Fungi or viruses can cause the disease. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including

Art Unit: 1614

staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1 and IL-18, and IFN- $\gamma$ .

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma, and bronchitis.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium). Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures

Art Unit: 1614

or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. Virtually any known infectious agent can cause it. Thus, if it were caused by *Haemophilus influenzae* or *Neisseria meningitis*, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also takes the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids are an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything that obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia, and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the exterior of the body. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when *Neisseria gonorrhoeae* is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially *Candida albicans*), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta-blockers.



Art Unit: 1614

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of *Mycobacterium paratuberculosis*. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as *Candida albicans*, dentures, chemotherapy, and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to *Lactobacillus* capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, *Ascaris* worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Art Unit: 1614

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis") (see printout of medline plus definition). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis, and cat-scratch disease. Treatment is thus to the underlying cause. For example, diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelmintic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from *Helicobacter pylori*. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee sting), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrown hairs, or pili

Art Unit: 1614

incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. The inflammation of acne is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus *Propionibacterium acnes*, which populate the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), that are formed enzymatically in response to e.g. injury.

Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching.

Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those, which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-

Art Unit: 1614

steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanism, and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation, furthermore various diseases mediated by p38. In *re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1920) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Appellant in his argument filed on August 03, 2007 takes the position that the numerous prior art references which have been made of record, namely USP 5,932,576, USP 5,593,992, USP 5,593,991 and USP 5,658,903, describe urea compounds of a similar structure and similar broad utility. Applicant alleges that most of these applications are assigned to pharmaceutical companies whose employees presumably are aware of what is known in medicine.

This argument is not found persuasive. Unlike the appellant's argument, none of the cited references provide similar urea structure of the instant compounds. Nor provides any specific guidance for determining the particular administration of regimens (e.g., dosages, timing, administration routes, etc...) necessary to treat all of the various diseases mediated by p38. Since no one has ever been used to treat any human diseases by the instant compounds, how is the skilled physician or artisan to know what dose to use for each of these different diseases. Are the identical doses to be used for treating these multiple complex disorders having unrelated manifestations? There is both an in vitro assay and an in vivo assay and it is unclear if these

assays correlate to all of the diseases encompassed by the claims. There is sufficient number of working examples of treatment of any diseases, animals or man.

Appellant in his argument filed on August 03, 2007 takes the position that all exemplified compounds are said to have IC50 values ranging from 1 nM to 10microM on page 75. Applicant alleges that no evidence has been presented by the examiner that his assay employed is not highly predictive for pharmaceutical use.

This argument is not found persuasive. As discussed above, since no one has ever been used to treat any human diseases by the instant compounds, how is the skilled physician or artisan to know what dose to use for each of these different diseases. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals. See *Ex parte Maas*, 9 USPQ2d 1746.

Appellant in his argument filed on August 03, 2007 takes the position that the instant invention can be determined by routine tests which are performed on a day to day basis on various compounds.

This argument is not found persuasive. As discussed above, the art of developing and testing pharmacological drugs, for example "cytokine mediated diseases" (broadly "m38 mitogen-activated protein kinase" mediated disease such as asthma, interstitial lung disease, pulmonary fibrosis and pneumonia and tuberculosis), particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used

Art Unit: 1614

to treat said disease conditions mediated by p38. For instance, Gura et al. cited for evidentiary purposes, teaches that researches face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further tech that since formal screening began in 1955, many thousands of drugs have shown activity in either in cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraph). It is noted that the pharmaceutical is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson et al., also cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects. Because of the known unpredictability of the art and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for all diseases mediated by p38 as inferred in the claims and contemplated by the specification.

Appellant in his argument filed on August 03, 2007 takes the position that Appellants have disclosed that all of the exemplified compounds are effective inhibitors of p38 on page 75 of the specification and that no further disclosure is necessary. Appellants allege that it is not necessary to report the relative values or correlate the structure of the compounds tested with the

relative activity to enable one skilled in the art to make and use the invention since each compound is active.

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Appellant in his argument filed February 02, 2007 takes the position that the specification does reasonably provide enablement for treating diseases "mediated by p38" using the compounds of formula I and does enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with theses claims. Appellant asserts that the rejection is improperly based on bare allegations and conclusions, and that there is no evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds

without undue experimentation. In appellants' Response filed February 02, 2007 (page 3, para. 2 to bridging page 4, para. 1 and page 5, para. 4 to bridging page 6, para. 1), appellant stated:

The specification cites a number of publications on pages 2-5, which are representative of the state of the art at the time of the invention. These publications have correlated TNF production and MMP production with a number of diseases. Since inhibition of p38 leads to the inhibition of TNF and MMP production, the p38 inhibitors of this invention will be useful in treating these diseases. No evidence has been presented to refute the findings or conclusions made in these publications or the present application. No evidence has been presented that any compounds of this invention, as inhibitors of p38, would not be effective in treating the diseases defined by this functional language. Furthermore, no evidence has been presented of the "undue experimentation" allegedly necessary to practice the invention commensurate in scope with the claims.

Only unsupported allegations and conclusions regarding the state of the art are provided to support the rejection such as, "There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated through p38 or (ii) all types of diseases other than cancer that are mediated by p38." Appellants wish to draw attention to US Patent No. 5,932,576, which contains claims to treating p38 mediated diseases using other small molecule compounds. The inventors of the '576 patent disclose the ability of the named compounds to inhibit p38 through in-vitro and in-vivo assays, as do the Appellants in their application. Others have defined the treatment of numerous inflammatory diseases using functional language similar to that used here. For example, US Pat. Nos. 5,593,991 and 5,593,992 claim the treatment of "cytokine mediated diseases," with small molecules, the activity of which is demonstrated by in-vitro assays. Therefore, contrary to the Examiner's allegation, those skilled in the art have recognized and claimed that certain compounds can be effective for treating all types of diseases mediated by p38.

In any event, the specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of the diseases identified (see pages 22-26). The specification also provides dosage ranges for the various methods of administration (see



Art Unit: 1614

pages 26-27). In fact, the specification provides more than it needs to, e.g., *in vitro* p38 kinase assays (and IC<sub>50</sub> data) and *in vivo* assays. In similar fashion, one of ordinary skill in the art, by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various diseases. This is absolutely routine in the field. Thus, appellants have provided more than adequate guidance (and examples) to enable the claimed invention. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited diseases with a compound of this invention.

Appellant's argument is not found persuasive. Contrary to the appellant's allegation, the examiner have cited various documents to support the examiner's position in determining why the instant invention does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Particularly, the cited post-dated documents by the examiner, for example Chialda et al., Respiratory Research 2005, 6:36, pp.1-19 and Kapoun et al., Molecular Pharmacology, abstract, 2006, www.molpharmaspetjournals.org, teaches that the inhibition of p38 is not enabling for the treatment of asthma and pulmonary fibrosis which fall within the scope of broadly claimed "disease mediated by p38" (see page 7, lines 1-2 of the specification). Chialda et al. discloses that inhibition of p38 seems to be an unlikely target for anti-inflammatory therapy for asthma whereas Kapoun et al. discloses p38 activation is not involved in pathogenesis of pulmonary fibrosis. See abstract, "Results" and "Conclusion".

Furthermore, the examiner had provided with supporting evidences, for example Feldmann, M., Nature Immunolgy, 2001, Vol. 2, No. 9, pp. 771-773, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9<sup>th</sup> ed., 1996, pp.51, Cecil Textbook of Medicine, 20<sup>th</sup>

Art Unit: 1614

Edition, Vol. 1, 1997 and Dumas et al., *Biorganic & Medicinal Chemistry Letters*, 10, 2000, pp. 2047-2050, to show (i) the unpredictability in art in designing drug that blocks p38 due to significant drug toxicity in human (page 772, column 3, lines 8-11 of the Feldman) or possible drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharmaceutical composition (page 51 of the Goodman & Gilman), (ii) the general recognition in the art that sites of cancers are different for each type, as are diagnosis and treatment (page 1004 of the Cecil Textbook of Medicine) and (iii) the modification of urea core group with different substituents would have different physiological activity, respectively.

As evidenced by the cited references by the examiner (see also van den Blink et al., *The American Association of Immunologists*, 2001, 166:582-587 for your reference), the requisite nexus between p38 inhibition and in vivo assessment of usefulness of p38 inhibition as anti-cytokine and anti-proteolytic enzyme in patients with the broadly defined "a disease mediated by p38" including asthma, pulmonary fibrosis and infectious disease (e.g., pneumonia and tuberculosis), other than rheumatoid arthritis, osteoarthritis and septic arthritis, was not known at the time of the invention was made. As a result, one of skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Examiner respectfully points out that in the determination of enablement one must take into account the guidance of the specification and the working examples (if any) presented in the specification. Appellant have not specifically described the compounds tested in the p38 assay or LPS induced TNF $\alpha$  production mouse model, they have not correlated the structure of the compounds tested with their relative activity in said assays and they have not tested the

Art Unit: 1614

compounds in any disease condition as claimed. If one is to interpret Tables 1-8 as being the “All compounds exemplified...”, then Tables discloses only 37 compounds wherein the A portion of the claimed compounds is a substituted 4-ter-butylpyrazolyl component and the B portion of the claimed compounds is a mono or di-substituted benzene ring (e.g., quinolyl or isoquinolyl).

Thus, the claimed compounds of Formula I, which have been shown to encompass an inordinate amount of compounds, would be represented by only 38 compounds with only 2 distinct cores (37 compounds with the A portion a 4-tert-butylpyrazolyl component and the B portion a mono or di-substituted benzene ring (e.g., quinolyl or isoquinolyl)). Further these compounds, if taken as exemplifying the compounds in the p38 assay and LPS assay, still are not correlated with treatment of “a disease mediated by p38” as claimed. Thus, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of working examples, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue “painstaking experimentation study” to use for treatment of “ a disease mediated by p38” with the compounds of Formula I that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. “the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation

Art Unit: 1614

should proceed.” In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

In response to Appellant’s argument that the provisional double patenting rejection is not ripe for review, the examiner recognizes that appellant cannot strip the board of its jurisdiction simply by failing to argue the merits. See E.g., In re Longi, 759 F.2d 887, 892, 225 USPQ645, 648 (Fed. Cir. 1985) (double patenting rejection over claims of three copending applications affirmed on the merits); In re Mott, 539 F.2d 1291, 1296, 190 USPQ 536, 541 (CCPA 1976) (double patenting rejection under 37 CFR § 101 over claims in a copending application was held correct on the merits but reversed because rejection was made final rather than provisional); In re Wetterau, 356 F.2d 556,558, 148 USPQ 499, 501 (CCPA 1966) (affirming provisional double patenting rejection over claims in a copending application on the merits). Accordingly, in absence of any argument, the examiner maintains that claims 50 and 52-56 are rejected provisionally under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776, 935 or claims 1, 3-4 and 7-11 of copending US. Application No. 10/086417.

**(11) *Related Proceedings Appendix***

The appellant’s statement of related proceedings appendix in the brief is correct. There are no decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c) (1) (ii) of this section.

For the above reasons, it is believed that the rejections should be sustained.

Art Unit: 1614

Respectfully submitted,

Brian Kwon:bk  
October 16, 2007

BRIAN-YONG S. KWON  
PRIMARY EXAMINER




Conferees

Ardin Marschel, Johann Richter



ARDIN H. MARSCHEL  
SUPERVISORY PATENT EXAMINER

Jacques Dumas et al.  
400 Morgan Lane  
West Haven, CT 06516



JOHANN RICHTER  
SUPERVISORY PATENT EXAMINER  
GROUP 16.3